Samarium Diiodide Mediated Reductive Coupling of Epoxides and Carbonyl Compounds: A New Stereocontrolled Synthesis of *C*-Glycosides from 1,2-Anhydro Sugars**

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Dedicated to Professor Antonio Gómez-Sánchez on the occasion of his 75th birthday

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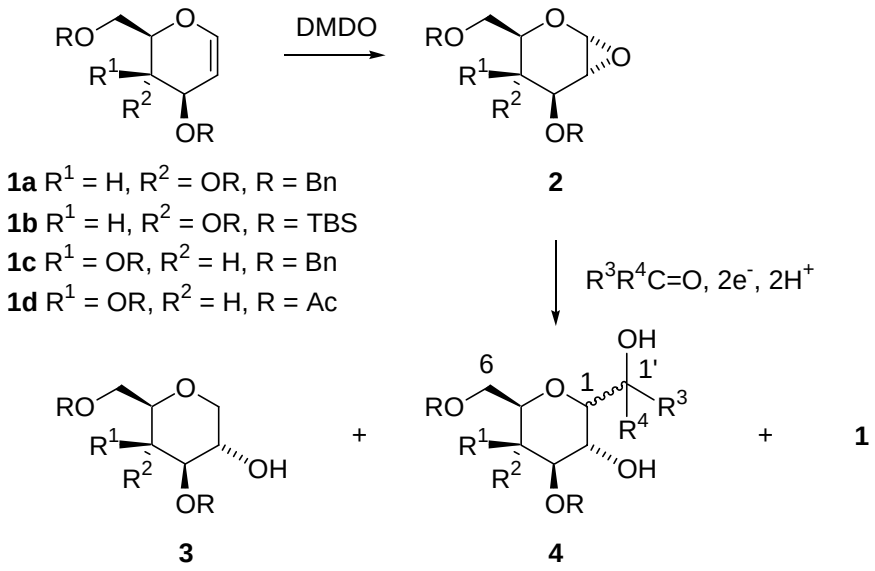
The significant advances in the understanding of the biological function of carbohydrates and glycoconjugates achieved during the last two decades have stimulated the development of glycomimetics as fundamental tools for biological research and as potential agents for therapeutic intervention.[1] *C*-Glycosides are of special relevance in this context due to their resistance to hydrolysis and to their occurrence in a number of natural products with interesting biological activity. Methods for their preparation using anomeric anions, cations, radicals, and carbenes have been extensively studied.[2] 1,2-Anhydro

sugars, readily available and well-known donors for the stereoselective preparation of *O*-glycosides,[3] have also found application in the stereoselective synthesis of *C*-glycosides.[2] Due to their electrophilic nature, in all examples described to date 1,2-anhydro sugars have been reacted with metalated *C*-nucleophilic partners, which are often unstable and not readily available with a wide range of functionality. The regioselective and stereodefined umpolung of 1,2-anhydro sugars into nucleophilic *C*-glycosyl donors by reductive metalation could greatly extend the scope of these useful donors allowing the introduction of an expanded set of substituents at the anomeric position in a stereoselective way.[4]



Scheme 1. Synthesis of *C*-glycosides from glycals by a one-pot DMDO oxidation and intermolecular reductive coupling reaction with carbonyl compounds.

To test the feasibility of this approach, we performed exploratory experiments with epoxide **2a**, readily available from protected D-glucal **1a** by DMDO oxidation (Scheme 1).[9] Initial attempts to couple **2a** to isobutyraldehyde[10] in the presence of $[Cp_2TiCl]_2$[10o,11] as reducing agent produced only minor amounts of *C*-glycoside **5**[5,8] (<20%) as a 1:1 mixture of α-diastereoisomers, irrespective of temperature (-78 °C to rt) and order of addition of reagents (Table 1, entry 1). The major products obtained under these conditions were the corresponding glycal **1a** and the 1-deoxy pyranose **3a**. We next assayed samarium(II) diiodide as the reducing agent. Gratifyingly, addition of isobutyraldehyde (4 equiv) to a THF solution of SmI_2 containing a catalytic amount of NiI_2 (1 mol%),[6p,6q,12,13] at –78 °C, followed immediately by dropwise addition of a THF solution of crude **2a** afforded the α-*C*-glycoside **5a** in 60% overall yield as a 4:1 mixture of diastereoisomers[14] together with minor amounts of **1a** and **3a** (Table 1, entry 2). This two-step/one-pot DMDO oxidation-SmI_2 reduction sequence was successfully applied to the coupling of differently protected glycals **1a**-**d** with a series of simple aldehydes and ketones yielding *C*-glycosides of D-*gluco* and D-*galacto* configuration in moderate to good overall yields (Table 1).

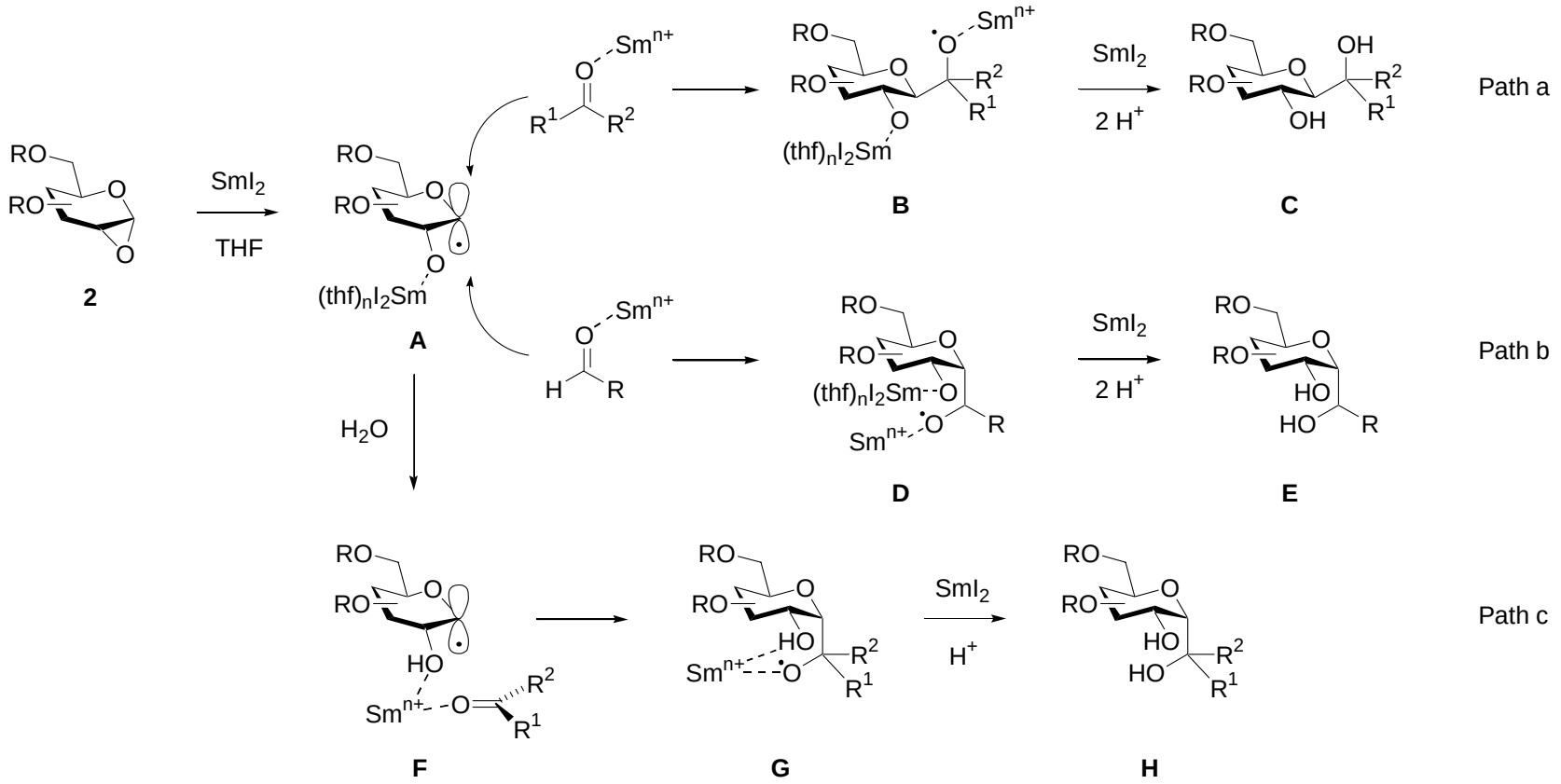
Some unique features of this new reductive coupling process are worth emphasizing. First, it shows wide protecting group compatibility due to the very mild reaction conditions. Thus, apart from benzyl and silyl ethers, ester groups on the glycal are completely stable under the reaction conditions (Table 1, entries 5, 7, 14). Second, the α/β-stereoselectivity of the reaction is subtly sensitive to steric effects. In contrast to other reductive samaration procedures,[6] α-C-glycosides are predominantly or exclusively obtained with aldehydes (Table 1, entries 1-5, 7) independently of the protecting group arrangement and configuration of the starting glycal, while ketones give the corresponding β-isomers as major products (Table 1, entries 8, 10, 11, 13, 15, 16, 20).[15]

The new reductive coupling procedure was also successfully applied to β-epoxide **16**[16] affording *C*-glycosides of D-*manno* configuration in good yields (Table 2). In this case, α-*C*-glycosides are selectively obtained both with aldehydes and ketones.

A series of control experiments were carried out for mechanistic studies that attest to the radical character of the C-C bond-forming step. First, fair yields of *C*-glycosides were still obtained performing the reaction in the presence of a large excess (10 mole-equiv) of D_2O

(Table 1, entries 6, 9, 12, 14, 17; Table 2, entries 2, 4). Unexpectedly, the “proton” source affected the diastereoselectivity of the reaction. Thus, 1,2-cis *C*-glycosides are selectively formed under these protic conditions in all cases.[17] Second and not surprisingly, addition of 10 equiv of *t*BuSH, a good hydrogen donor, severely affected the yield of *C*-glycoside giving the corresponding 1-deoxy-pyranose as mayor product (Table 1, entry 19).

A possible mechanistic rationalization for the above observations is illustrated in Scheme 3 for the case of 1,2-anhydro sugars **2**. Single electron transfer (SET) from SmI_2 to the epoxide group[18] of **2** regioselectively leads to an α-anomeric radical intermediate in the form of a solvated samarium(III) alkoxide **A**. Intermolecular radical addition of **A** to the Lewis acid (Sm^{2+} or Sm^{3+})-activated carbonyl group and subsequent (or concomitant) kinetic trapping of the generated alkoxyl radical (**B** or **D**) by a second SET from another molecule of SmI_2 (possibly by inner-sphere ET[19] from a chelated Sm^{2+}) produces the *C*-glycoside after hydrolysis. Destabilizing steric interactions between the solvated samarium(III) alkoxide at C-2 in **A** and the incoming complexed carbonyl moiety along the kinetically favoured axial trajectory of attack[20] (Path b) is more severe in the case of ketones, which could



Scheme 2. Proposed mechanistic pathway for the reductive coupling of 1,2-anydro sugars with carbonyl compounds promoted by SmI_2.

explain a preferential 1,2-trans approach in their case (Path a). Under protic conditions (Path c), fast protonation of the samarium alkoxide at C-2 of **A** allows a hydroxyl-directed[6i,21] approach of the Lewis acid activated carbonyl (**F**) generating the 1,2-cis *C*-glycoside (**H**) predominantly. A similar mechanistic rationalization can be proposed for the couplings of the 1,2-anhydro-D-manno-pyranose **16**. Glycal and 1-deoxypyranose are likely formed by competitive reduction of the anomeric radical **A** to an anomeric carbanion followed by β-elimination or protonation, respectively.[22]

In summary, we have developed an efficient preparation of *C*-glycosides by a new intermolecular reductive coupling reaction of 1,2-anhydro sugars with carbonyl compounds promoted by samarium(II) diiodide. Outstanding features of the new approach are the following: 1) the starting 1,2-anhydro sugars are ready availability with different stereochemistry, 2) good overall yields of *C*-glycoside are obtained independently of the configuration of the starting 1,2-anhydro sugar, 3) the very mild reaction conditions allow a wide *O*-protecting group compatibility, 4) the stereoselectivity of the reaction is complementary with other syntheses of *C*-glycosides mediated by SmI_2, 5) *C*-glycosides with a free hydroxyl group at C-2 are directly obtained facilitating further selective functionalizations,

and 6) the stereoselectivity of the reaction can be significantly modified by adding a proton source. The extension of this process to other radical acceptors and its application to the solution and solid phase synthesis of *C*-glycosydic analogues of biologically important natural glycosides are being actively pursued in our laboratory.

Experimental Section

General procedure for the preparation of *C*-glycosides: To a freshly prepared solution of SmI_2 (6 equiv) in THF containing 1 mol% of NiI_2 at –78 °C under argon was added in one portion a carbonyl compound (4 equiv) followed immediately by dropwise addition of a 0.1M THF solution of the crude 1,2-anhydro sugar[9,16] (1 equiv) over 30 min. After stirring at –78 °C for 1.5h, the reaction mixture was allowed to slowly attain rt (1h). A 10:1 mixture of saturated aqueous Rochelle salt and saturated aqueous $NaHCO_3$ was added and the mixture was extracted with EtOAc (3x). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and evaporated to dryness under reduced pressure. The residue was chromatographed on silica gel to obtain the products.

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[13] In the absence of NiI_2, yields of *C*-glycoside were in general 10-15% lower.

[14] The configuration of the new stereocenters was determined from ^{1}H NMR and n.O.e. studies of the corresponding 1′,2-di-*O*-isopropylidene acetals (see Scheme 1 for numbering system).

[15] Interestingly, reductive samariation of anomeric sulfones of 2-deoxy-2-acetamido pyranoses in the presence of aldehydes or ketones also affords 1,2-cis *C*-glycosides preferentially.[6f,j-l]

[16] Prepared following a literature procedure and used without purification: Y. Du, F. Kong, *J. Carbohydr. Chem.* **1995**, *14*, 341.

[17] In general, increased amounts of glycal and/or 1-deoxypyranose are formed under these conditions.

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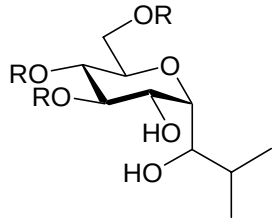
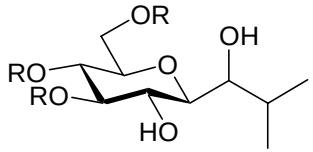
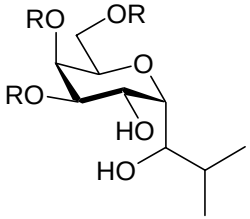
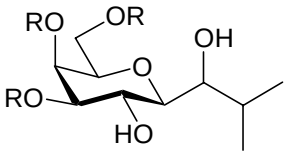
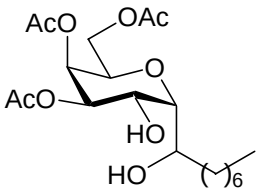
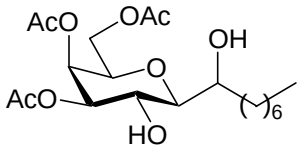
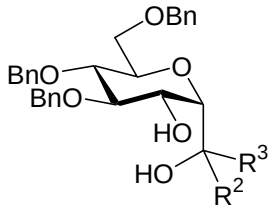
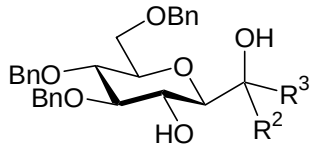
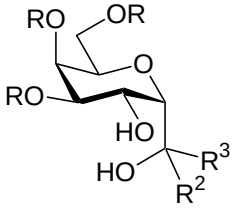
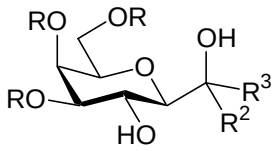
[22] 1-Monodeuterated 1-deoxypyranose (>80% deuterium incorporation by ^{1}H NMR analysis) is obtained when the coupling is performed in the presence of D_2O. Interestingly, deuterium incorporation is stereospecific. Thus, α-deuterated **3** and β-deuterated **17** are exclusively formed from α-epoxides **2** and β-epoxide **16**, respectively, as expected for a (chelated) 1,2-*cis* anomeric organosamarium intermediate. The corresponding 1,2-*trans* organosamarium should suffer a fast β-elimination to give the glycal. We believe that our observations cast some doubts on the commonly accepted carbanionic nature of other *C*-glycoside syntheses mediated by SmI_2[6] and the assumption of a preferred *syn*-elimination pathway[6c,i] for organosamarium compounds, unprecedented for other metal carbanions.

Table 1. One-pot DMDO oxidation-SmI_2 reductive coupling synthesis of *C*-glycosides from glycals and carbonyl compounds.

Entry	Glycal	Carbonyl compound	*C*-Glycoside		Glycal	1-Deoxy pyranose
			Yield[a] (diastereoisomer ratio)			
						
1	**1a**	isobutyraldehyde	**5a**[b] 15-20%[c] (1′*R*/1′*S* = 1:1)	**5b** ND[c,d]	**1a** 35-45%[c]	**3a** 25-40%[c]
2			60% (1′*R*/1′*S* = 4:1)	ND	12%	15%
3	**1b**	isobutyraldehyde	**6a** 67% (1′*R*/1′*S* = 1.5:1)	**6b** ND	**1b** 27%	**3b** ND

Entry	Glycal	Carbonyl compound	*C*-Glycoside		Glycal	1-Deoxy pyranose
			Yield[a] (diastereoisomer ratio)			
						
4	**1c**	isobutyraldehyde	**7a**[e] 76% (1′*R*/1′*S* = 2.5:1)	**7b**[f,g] ND	**1c** 6%	**3c** 14%
5	**1d**	isobutyraldehyde	**8a** 73% (1′*R*/1′*S* = 5:1)	**8b**[g] 9%	**1d** 8%	**3d** 7%
6			61%[h] (1′*R*/1′*S* = 9:1)	ND[h]	12%[h]	14%[h,i]
						
7	**1d**	1-octanal	**9a** 52%	**9b**[j] 18%	**1d** 16%	**3d** 2%

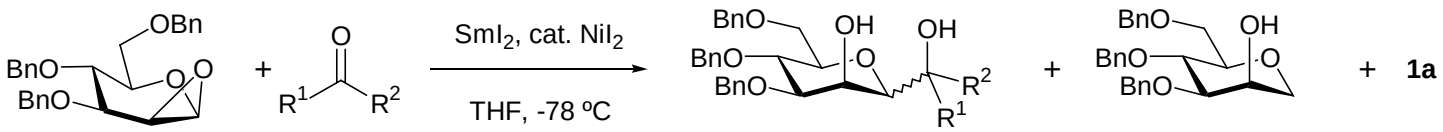
Entry	Glycal	Carbonyl compound	*C*-Glycoside	Glycal	1-Deoxy pyranose
			Yield[a] (diastereoisomer ratio)		
			(1′*R*/1′*S* = 6:1)		
					
8	**1a**	acetone	**10a** 12%	**10b** 64%	**1a** 3%	**3a** 8%
9			53%[h]	10%[h]	23%[h]	13%[h,i]
			(R^2 = R^3 = Me)			
10	**1a**	3-pentanone	**11a** 5%	**11b** 60%	**1a** 13%	**3a** 22%
			R^2 = R^3 = Et			
11	**1a**	cyclohexanone	**12a**[f] 12%	**12b**[f] 48%	**1a** 3%	**3a** 32%
12			51%[h]	8%[h]	20%[h]	17%[h,i]
			R^2,R^3 = $(CH_2)_5$			

Entry	Glycal	Carbonyl compound	*C*-Glycoside		Glycal	1-Deoxy pyranose
			Yield[a] (diastereoisomer ratio)			
						
13	**1c**	acetone	**13a** ND	**13b** 70%	**1c** 2%	**3c** 16%
14			40%[h]	2%[h]	42%[h]	2%[h,i]
			$R^2 = R^3 = Me$			
15	**1c**	cyclohexanone	**14a** ND	**14b**[f] 77%	**1c** 3%	**3c** 18%
			$R^2, R^3 = (CH_2)_5$			
16	**1d**	acetone	**15a** 15%	**15b** 46%	**1d** 9%	**3d** 9%
17			40%[h]	6%[h]	15%[h]	24%[h,i]
18			44%[k]	8%[k]	19%[k]	12%[k]
19			5%[l]	7%[l]	8%[l]	43%[l]
			$R^2 = R^3 = Me$			

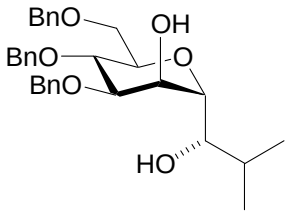
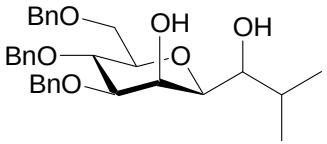
Entry	Glycal	Carbonyl compound	*C*-Glycoside		Glycal	1-Deoxy pyranose
			Yield[a] (diastereoisomer ratio)			
20	**1d**	3-pentanone	**16a** 8%	**16b** 48%	**1d** 14%	**3d** 15%
			$R^2 = R^3 = Et$			

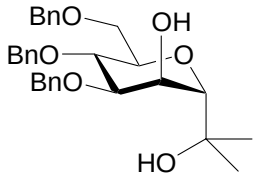
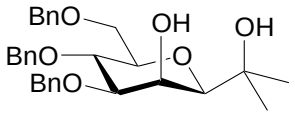
[a] Overall yields of isolated products from starting glycal; diastereoisomeric ratios as determined by ^{1}H NMR of the crude reaction mixtures. [b] Ref. [5a,8]. [c] Reaction performed using $[Cp_2TiCl]_2$ (see text). [d] Not detected. [e] Ref. [5b]. [f] Ref. [6c,i]. [g] Single diastereoisomer (stereochemistry at C-1′ not determined). [h] Reaction performed in the presence of 10 equiv of D_2O. [i] ^{1}H NMR analysis showed that compound **3** was >80% α-monodeuterated at C-1. [j] 1:1 Mixture of diastereoisomers at C-1′. [k] Reaction performed in the presence of 2 equiv of D_2O. [l] Reaction performed in the presence of 10 equiv of *t*BuSH.

Table 2. SmI_2-promoted synthesis of *C*-glycosides from glycal **16**.



16 **17**

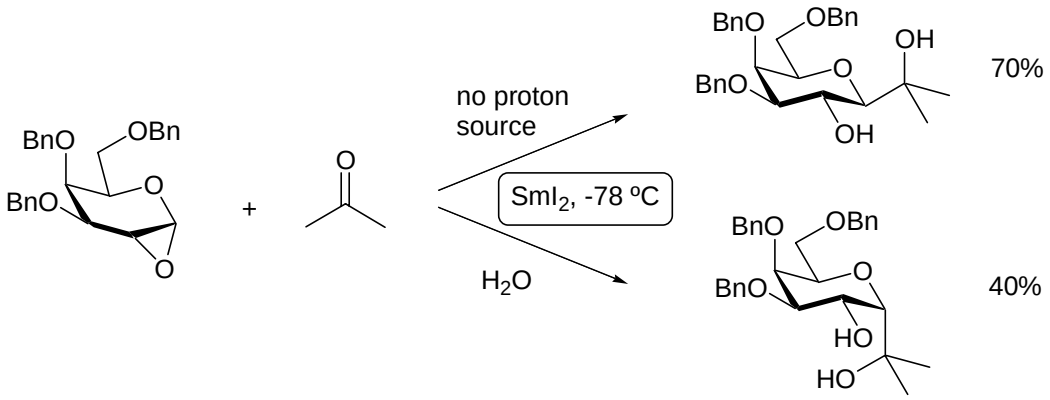
Entry	Carbonyl compound	*C*-Glycoside		Glycal	1-Deoxy sugar
		Yield[a] (diastereoisomer ratio)			
					
1	isobutyraldehyde	**18a**[b] 68%	**18b** ND	**1a** 9%	**17** 12%
2		8%[c]	25%[c]	9%[c]	34%[c,d]

Entry	Carbonyl compound	*C*-Glycoside		Glycal	1-Deoxy sugar
		Yield[a] (diastereoisomer ratio)			
					
3	acetone	**19a** 63%	**19b** ND	**1a** 9%	**17** 11%
4		11%[c]	27%[c]	9%[c]	26%[c,d]

[a] Overall yields of isolated products from crude; diastereoisomeric ratios as determined by ^{1}H NMR of the crude reaction mixtures. [b] Ref. [6i]. [c] Reaction performed in the presence of 10 equiv of D_2O. [d] ^{1}H NMR analysis showed that compound **17** was >80% β-monodeuterated at C-1.

Short text for the Table of Contents:

A new synthesis of C-glycosides: 1,2-anhydro sugars can be cross-coupled with aldehydes and ketones under very mild conditions to give *C*-glycosides in good yield in a new radical reaction mediated by SmI_2.



Keywords: C glycosides, radical reactions, electron transfer, samarium